Oxygen tension - based indices of oxygenation

By Alex Yartsev - 08/06/2015
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This chapter is most relevant to Section F9(iii) from the 2023 CICM Primary Syllabus, which expects the exam candidates to *"understand respiratory equations that describe ventilation, perfusion, blood flow and respiratory mechanics"*. The alveolar gas equation seemed suficiently special to merit its own page, but all the other equations were lumped together and discussed here. CICM have never asked a primary exam question about this, but it came up randomly in the Fellowship exam, in Question 17 from the second paper of 2007 and Question 3 from the first paper of 2006. A brief revision chapter is embedded in the Part Two notes, in case the time-poor Part One candidate decides to omit this part of their preparation.

In summary:

The tension-based indices of oxygenation are:

- **A-a gradient**
  - Magnitude of the PO_2 gradient between the alveolus and the arterial blood, expressed in mmHg
  - Calculated using the alveolar gas equation and PaO_2 measurment
  - Normal value is 7mmHg in the young, and 14 mmHg in the old.
- **a/A ratio**
  - A ratio of arterial to alveolar PaO_2
  - A pO_2(a/A) of over 75% is probably normal.
  - Unlike the other indices, it is unaffected by FiO_2 or barometric pressure.
  - A normal a/A ratio in a hypoxic patient **must be** due to alveolar hypoventilation or low atmospheric pressure.
  - A low a/A ratio may be due to any of the following:
    - V/Q mismatch, eg shunt - intrapulmonary or intracardiac
    - Diffusion defect
    - Increased oxygen extraction ratio
- **PaO_2/FiO_2 ratio**
  - Ratio of arterial oxygen to inspired oxygen
  - Simple to calculate
  - Acts as a risk stratification tool
  - Insensitive to changes in atmospheric pressure
  - Unable to discriminate between different aetiologies of hypoxia
- **Respiratory index (RI) (RI = pO2(A-a)/*p*O2(a))**

- This is the A-a gradient divided by the PaO_2
- Similar in its use to the a/A ratio
- A normal RI is anything under 0.4,

This is not a simple topic; in fact it took a group of specialists a large hard-cover publication to make it complicated, prompting the editor of the BMJ to remark that "*For every complex problem, there is a solution that is simple ... and wrong*". The best reference discussing these indices seems to be *Essentials of Oxygenation: Implication for Clinical Practice* by Ahrens et al, particularly their Chapter 3 (*Intrapulmonary Shunting*). Another good comparison of these various indices is available for the paying customer of *Acta Anaesthesiologica Scandinavica.*

Broadly, one can say that two things are true:

> Indices based on oxygen tension are popular because of simplicity, not validity.
>
> The best index of pulmonary oxygen transfer is *the measured intrapulmonary shunt fraction.*

The more familiar indices of oxygenation are:

- A-a gradient
- a/A ratio
- PaO2/FIO2 ratio
- Respiratory index (RI) (RI = pO2(A-a)/*p*O2(a)).

These are *tension*-based indices; in that they require partial pressures of gases to be calculated from the alveolar gas equation, and are therefore subject to numerous influences as well as errors in the estimation of the respiratory quotient (RQ) which is a pain in the arse to measure directly.

The tension-based indices differ from the *concentration-based* index like *F*Shunt. It is discussed in greater detail elsewhere; suffice to say, it relies on arterial oxygen content rather than partial pressure, and requires an assumption to be made regarding the arterio-venous oxygen content difference being 30-50ml/L, which is not a robust assumption in the hideously diseased ICU patient.

Factors which influence the tension-based indices of oxygenation

One might imagine that in a perfect world all the alveolar gas would gladly exchange into the blood, and there would be no difference in oxygen between them. Unfortunately, even with a completely normal alveolar gas exchange, there is a certain difference - inevitably, arterial pO_2 is going to be lower.

Why, might one ask?

Numerous factors are in play. This was explored in depth by Kresten Mellemgaard in 1966. 80 normal subjects were investigated. Mellemgaard found that the A-a difference could be attributed to the following contributors:

- Right-to-left shunt in the lungs (minute contribution)
- Drainage from bronchial and thebesian veins into the left atrium (50% contribution)
- Defect of alveolar gas exchange (~50% contribution in the young, but increasing with age)

Hills further elaborated on this in 1971. It looks like a very nice, heavily detailed article, but it is not available to me. Fortunately, Nunn's respiratory physiology textbook has a nice chapter on this topic (Ch. 11 of the 8th edition, *"Oxygen"*). It's so nice that some of the diagrams were borrowed by the editors of Oh's Manual (in other words, if a book has influenced CICM examiners, it is probably worth reading before the exam).

In short, and at risk of wrecking SEO through repetition, the factors which influence oxygen tension-based indices are:

- **Venous admixture, or "shunt"** - as mentioned above, and discussed in greater detail elsewhere, shunt is the fraction of pulmonary blood flow which is not exposed to fresh gas. The influence of venous admixture on the A-a difference varies with the magnitude of shunt and with the FiO_2 level.
- **V/Q scatter**: the effect of blood flowing through a heterogeneously ventilated/perfused lung. Consider underventilated but overperfused alveoli. Obviously they are going to contribute a lot of hypoxic blood.

Think: blood flowing through overventilated but *under*perfused units will never be able to compensate, as its volume is lower.

- **Congenital heart disease** with right-to-left shunting is a possibility that should be mentioned, as it allows the right heart to eject into the left circulation.
- **Cardiac output** can increase the A-a difference when it happens to be unusually high, particularly when the diffusion is impaired. Blood travels through the alveoli faster then oxygen can diffuse into them; this is seen in the exercise-induced hypoxia of pulmonary fibrosis patients.
- **FiO_2**: with a large shunt, an increase in alveolar O_2 will have little influence on the arterial O_2, as the shunted blood has no access to oxygen. But the alveolar gas equation will give a high alveolar O_2 concentration. Keep increasing the FiO_2, and the alveolar O_2 keeps increasing, but the arterial O_2 does not - thus, the A-a difference grows *without any change to the intrapulmonary shunt fraction.*
- **Temperature** is a minor player, as it influences the solubility of oxygen in blood - a hideously hypothermic patient's blood can contain more dissolved oxygen, whereas the cold does nothing for alveolar oxygen content - and so the A-a difference increases slightly if the total oxygen content remains the same. Let's break this up a little bit. Cold blood, specifically cold water, can contain a lot more oxygen. If the oxygen content in the blood remains stable, this improvement in solubility results in a decreased partial pressure, as more of the gas is inclined to remain in the solution. Thus, the PaO_2 decreases slightly, while the PAO_2 remains stable.
- **Increased alveolar ventilation (i.e decreased pCO_2)** results in an increased alveolar O_2 because the gas mixture of the alveolus obeys Dalton's Law. However, if all the factors influencing A-a gradient remain the same, the A-a gradient should increase in proportion to the alveolar O_2.
- **Oxygen extraction ratio** can throw off the A-a gradient. Consider a hypothetical patient with metabolism so sluggish that even after passing through their systemic circulation, their mixed venous oxygen content is only 1mmHg lower than the arterial. This sort of strange mutant will have a normal-looking A-a gradient even in the presence of significant lung pathology.

- **Weird stuff** cannot go unmentioned, such as venous drainage from lung tumours directly into the pulmonary veins, or AV malformations which form in the context of Osler-Rendu-Weber syndrome.

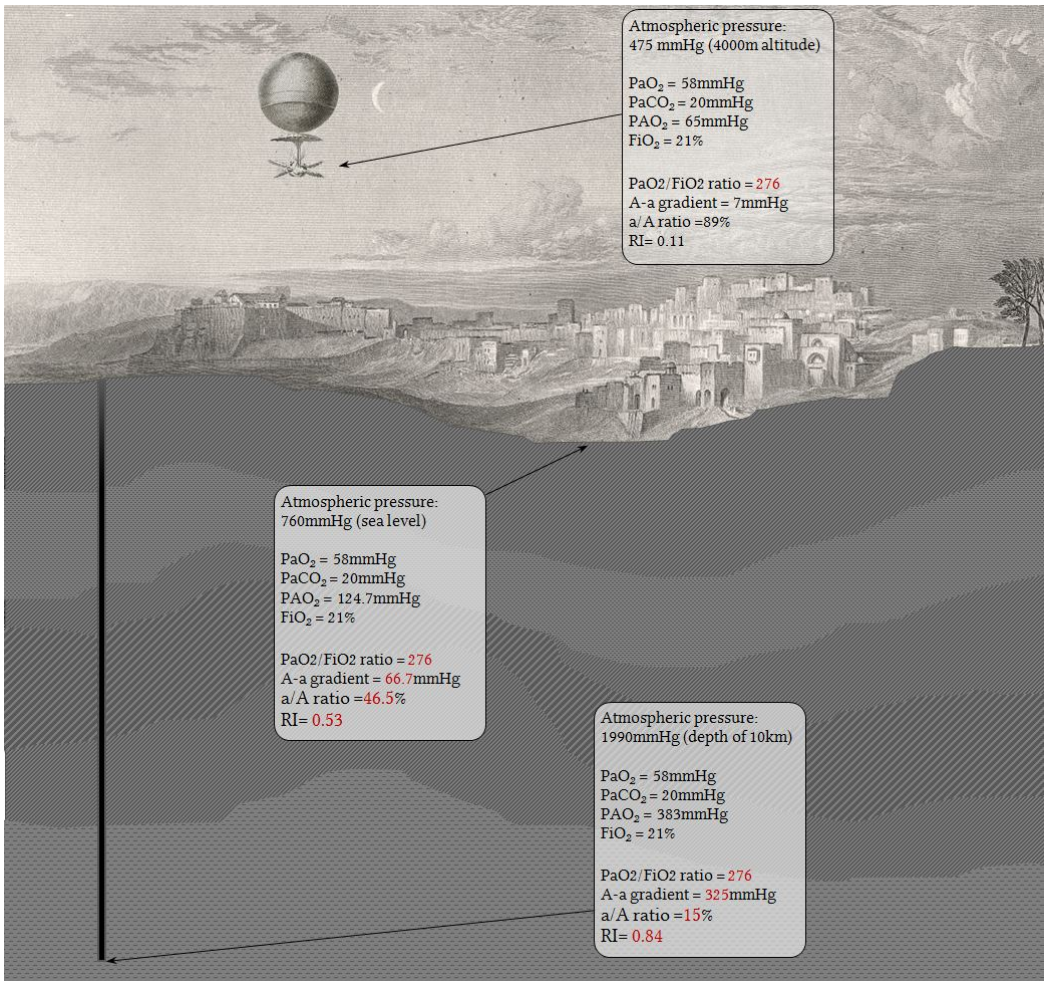
So, the A-a difference is increased, and you have all these potential reasons as to why. It is no wonder that indices based on it are criticised for being non-specific.

The PaO_2/FiO_2 ratio

This is generally held to be the easiest oxygenation index to calculate; in fact Oh's Manual admits that "its main advantage is simplicity". One only needs two variables, and one divides one by the other; anything over 500 is normal. However, in this simplicity lurks a danger.

Errors due to differences in atmospheric pressure

Because it uses raw partial pressure numbers, this index is susceptible to barometric horseplay.



Consider a young man involved in some sort of freakish helium balloon accident, trying to breathe a normal 21% oxygenated gas mixture at 4000m altitude. His atmospheric pressure is 475mmHg and the ideal alveolar O_2 is something like 65mmHg. Let us say he is able to generate an arterial O_2 of 58mmHg.

The PaO_2/FiO_2 ratio would be 65 ÷ 0.21, or 276- which would label this young man as fairly hypoxic. That might be accurate, but *his lungs are working just fine.* The A-a gradient would reveal that there is in fact only 7mmHg of difference between the alveoli and the arteries.

Conversely, the same young man, with the same findings, but at the bottom of a 10 kilometer mine shaft would find himself exposed to an atmospheric pressure of 1990mmHg. With exactly the same blood gas data, we would have exactly the same PaO_2/FiO_2 ratio (65 ÷ 0.21 = 276) . However, the alveolar O_2 would now be 383mmHg, giving us an A-a gradient of 325mmHg. In this situation, the PaO_2/FiO_2 ratio would be *underestimating* the severity of the gas exchange failure.

Failure to discriminate among different aetiologies

PaO_2/FiO_2 ratio does nothing but describe the relationship between inspired gas fraction and arterial gas tension. This is unhelpful in determining as to *why* this difference arose. At least the A-a gradient, though a totally blunt tool, can discriminate between alveolar hypoventilation and V/Q mismatch.

Utility as a risk stratification tool

Forgetting for a moment any discussion of *actual* utility, one should acknowledge that this index is in fact being used as a risk stratification tool. According to an extinct definition, "Acute Lung Injury" (ALI) is a PaO_2/FiO_2 ratio under 300, and in ARDS the ratio is under 200. The new "Berlin Definition" has not changed this very much. Rather, "ALI" as the descriptor of mildly damaged lungs has been abandoned, and instead the 300-200 ratio range is now "mild" ARDS, 200-100 is "moderate" and under 100 is "Severe". The associated mortality increase is quoted as 27%, 32% and 45% respectively.

The A-a gradient

The A-a gradient is essentially arterial (PaO_2) subtracted from alveolar (PAO_2). The resulting number is the magnitude of the gradient between the alveolus and the arterial blood, expressed in mmHg.

The normal value at 21% FiO_2 is 7mmHg in the young, and 14mmHg in the old (Kanber et al, 1968). There are several age-based formulae which can be used to determine what the expected A-a gradient is, at any given age:

> Normal A-a gradient = Age / 4 + 4 (in mmHg)

From LITFL and Part One, or

> Normal A-a gradient = (Age +10) / 4 (in mmHg)

(Sharma et al, 2019), or

> Normal A-a gradient = 2.5 + (0.21 * Age)

(Medscape, reference unknown)

This index is highly dependent on FiO_2 and shunt. Lets say you have one lung blocked up with pus, and the other lung pristine, generating a 50% shunt. With an unchanging shunt, you can go from a A-a gradient of 50 (PaO_2 50mmHg, PAO_2 100mmHg) to an A-a gradient of over 300 (PaO_2 50mmHg, PAO_2 377mmHg), all by changing the FiO2 from 21% to 60%.

Thus, one can only really rely on it in a patient breathing room air. It may be useful as a screening tool - one relaxes somewhat when the A-a gradient is normal on room air. One study of patients undergoing V/Q scans had revealed that only 1.8% of patients with a normal A-a gradient had a PE, and suggested that "*further diagnostic evaluation may be unnecessary in this subgroup of patients*". However, another similar study using angiography determined that "*various combinations of the a-a gradient and blood gas levels failed to exclude PE in more than 35% of patients with no prior cardiovascular disease and in 25% of patients with prior cardiovascular disease*". Thus, it may lull one into a false sense of security.

Of course, all this is in reference to ED patients. One may only interested in discriminating between those pleuritic chest pains who go home on clexane from those who go home with a lollypop.

An ICU population is somewhat different. What does an A-a gradient mean in the population of hypoxic critically ill patients? LITFL has a good page on the subject, which classifies hypoxia according to A-a gradient abnormalities:

Causes of Hypoxia Classified According to A-a Gradient	
Normal A-a gradient	*Raised A-a gradient*
• High $PaCO_2$ - i.e. alveolar hypoventilation • Low FiO_2 (eg. at altitude)	• V/Q mismatch (eg. shunt or dead space ventilation) • High FiO_2 • Diffusion defect • Intracardiac shunt • Increased oxygen extraction ratio (i.e. very hypoxic mixed venous blood returning to the lungs)

Realistically speaking, the A-a gradient is only able to confidently identify one specific cause of hypoxia, which is alveolar hypoventilation. This is the case because the Alveolar Gas Equation factors in the measured arterial CO_2 level.

The a/A ratio

The a/A ratio is is the PaO_2 divided by the PAO_2, and the ratio is offered as a percentage (i.e. there are [this many percent] of alveolar oxygen getting into the arterial circulation). The normal value is generally held to be anything greater than 75%.

It is said that the advantage of this over the standard A-a gradient is that it takes into account the changes in FiO_2 which is a major confounder of the A-a gradient.

Observe a hypothetical table of findings:

	On admission	Arrival to ICU	After intubation
PaO_2(mmHg)	70.9	86.7	470.7
$PaCO_2$(mmHg)	40	22	40
FiO_2(%)	21%	21%	100%
PAO_2 (mmHg)	99.9	122.2	663.0
PaO_2/FiO_2 ratio	337	412	470
A-a gradient	29	35.5	192.3
RI	0.41	0.41	0.41
a/A ratio	0.71	0.71	0.71

In this patient, the A-a gradient changed impressively - but the a/A ratio did not. This also demonstrates the reliance of A-a gradient on the FiO_2. In fact, observe the wild fluctuation in oxygenation indices: the P/F ratio is telling you the patient is improving, the A-a gradient is telling you they are getting worse, and the a/A ratio is convinced that the patient is exactly the same. At this point, a weaker person would become very disappointed by the tension-based oxygen indices.

In spite of this, the a/A ratio seems useful. Its utility in deciding on the

supplemental oxygen level has been validated in at least one case series.

However, it may not add very much to the calculation of the A-a gradient. Observe this series of room air gases of identically hypoxic patients:

	V/Q mismatch	Alveolar hypoventilation	Barometric weirdness
Atmospheric pressure	760	760	600
PaO_2(mmHg)	60	60	60
$PaCO_2$(mmHg)	20	60	40
FiO_2(%)	21%	21%	21%
PAO_2 (mmHg)	124.7	74.7	66.1
PaO_2/FiO_2 ratio	285	285	285
A-a gradient	64.7	**14.7**	**6.13**
a/A ratio	0.48	**0.8**	**0.91**

The a/A ratio and A-a gradient were both normal in the high altitude gas and in the hypercapneic patient.

Thus, both indices - when normal - can exclude V/Q mismatch, increased oxygen extraction ratio and diffusion defects as causes of hypoxia. The P/F ratio, blind to barometric pressure changes and pCO_2 differences, does not notice any difference between these patients.

The Respiratory Index (RI)

The "respiratory index" is simply the A-a gradient divided by the PaO_2. Thus, a normal RI is anything under 0.4, corresponding to an A-a gradient of around 40mmHg at 21% FiO_2 and a $PaCO_2$ around 40mmHg. This is the most "permissive" of the indices; according to the abovelisted numbers its range of normality ends at an arterial O_2 tension of around 60mmHg (where many of us would be uncomfortably breathless).

This index, like the a/A ratio, benefits from the use of the alveolar gas equation; its ability to compensate for changes in FiO_2 and $PaCO_2$ lend it a resilence which the A-a gradient lacks. As can be seen in the hypothetical list of ABG

results above, the RI and the a/A ratio both reflect the reality of an unchanging intrapulmonary shunt, while the other indices offer ridiculous and contradictory suggestions.

Neither literature searches nor personal reflection has thus far revealed any advantages of the RI over a/A ratio to this author. There may be none, and the two may be equivalent. In general the RI appears to be a neglected index, and even Ahrens' extensively detailed "*Essentials of Oxygenation*" refuses to discuss it at any length because it is "a less commonly used measure".

Comparison of tension-based indices

The CICM Fellowship examiners have interrogated this cognitive niche in a past paper - Question 17 from the second paper of 2007 asks, *"Outline the advantages and limitations of the A-a gradient and PaO2/FiO2 ratio as indices of pulmonary oxygen transfer"*. This may have something to do with Chapter 18 from Oh's Manual ("Monitoring oxygenation) by Thomas J Morgan and Balasubramanian Venkatesh, where *precisely that issue* is addressed on pages 148-149.

The college answer is a table, which - if retrofitted with extra indices - might resemble the following:

Indices of Pulmonary Oxygen Transfer: Advantages and Limitations			
Index	*Calculation*	*Advantages*	*Disadvantages*
A-a gradient	Alveolar gas equation	• Simple • Minimally invasive • May distinguish alveolar hypoventilation from all other causes of hypoxia • Required by	• The magnitude of the A-a gradient is highly dependent on FiO_2, especially in the presence of a large shunt • Age dependent (increases with age)

		APACHE II, III and IV	• Non-specific - influenced by numerous factors
PaO_2/FiO_2 ratio	Divison of inspired O_2 fraction by alveolar tension	• Simple • Minimally invasive • Required by APACHE IV • Used in severity stratification of ARDS	• Cannot distinguish between alveolar hypoventilation and other causes of hypoxia • Makes no attempt to incorporate changes in $PaCO_2$ • Unreliable unless FiO2 > 0.5 or PaO_2 < 100 • Not reliable in COPD because of V/Q mismatch • Barometric pressure dependent
a/A ratio	Arterial pO_2 divided by alveolar pO_2.	• Reasonably simple • Minimally invasive • May distinguish alveolar hypoventilation from all other causes of hypoxia • Independent of FiO_2 changes	• Age dependent (increases with age) • Non-specific - influenced by numerous factors • Oxygen tension based index
Respiratory index	A-a gradient divided by the PaO_2	• Reasonably simple • Minimally invasive • May distinguish alveolar hypoventilation from all other causes of hypoxia • Independent of FiO_2 changes	• No addiitonal advantages over the a/A ratio • Not commonly used; difficult to relate findings to management decision criteria or compare them to published studies.

Estimated shunt fraction (*F*shunt)	Shunt equation (using a Ca_{O2}-CV_{O2} difference of around 30-50ml/L, or 2.3 mmol/L)	• Oxygen content rather than oxygen tension based index • Minimally invasive- does not require mixed venous sampling • Independent of FiO_2 and $PaCO_2$ changes	• Assigned Ca_{O2}-CV_{O2} difference can be completely incorrect in critical illness, completely invalidating the calculations.
Measured intrapulmonary shunt (Qs/Qt)	Shunt equation	• Gold standard of shunt assesment • Empiric measurement; accounts for unpredictable influences on shunt.	• Maximally invasive (requires PA catheter) • Requires mixed venous sampling • Complex calculations involved • In V/Q mismatch without right-to-left shunt, venous admixture varies markedly with FiO_2 and virtually disappears at FiO_2>0.5.

In summary:

- Oxygen tension based indices are unreliable in the assessment of intrapulmonary shunt
- It seems there is no good substitute for the PA catheter for measuring intrapulmonary shunt.

Previous chapter: The alveolar gas equation

Next chapter: Interpretation of lung function tests

References

The Alveolar Gas Equation was first described in a famous work by Wallace Fenn, Hermann Rahn, and Arthur Otis.

Fenn, Wallace O., Hermann Rahn, and Arthur B. Otis. "A theoretical study of the composition of the alveolar air at altitude." *American Journal of Physiology--Legacy Content* 146.5 (1946): 637-653.

Device-specific information in all these ABG pages refers to the ABG machine used in my home unit.

Other machines may have different reference ranges and different symbols.

For my ABG analyser, one can examine this handy operations manual.

There is also an even more handy reference manual, but one needs to be an owner of this equipment before one can get hold of it. Its called the "989-963I ABL800 Reference Manual"

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However, it is not available as free full text.

Though the JAMA site is still paywalled, The Sociedad Uruguaya de Neonatologia Y Pediatria Intensiva have mirrored the Berlin Definition statement article for your viewing pleasure:

CV. Marco Ranieri, MD (2012). "The ARDS Definition Task Force*. Acute Respiratory Distress Syndrome: The Berlin Definition". JAMA 307 (23): 2526-2533.

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